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Comm.
Dr. Andervont
Dr. Gardner
Dr. Jacobson

CANCER

THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application for Research Grant
(Use extra pages as needed)

Date: 18 July, 1973.

1. Principal Investigator (give title and degrees): Dr. L.G.S. Rao, Ph.D.

2. Institution & address: Royal Infirmary, Glasgow, G4 0SF.

3. Department(s) where research will be done or collaboration provided: Department of Steroid Biochemistry.

4. Short title of study: Correlation of the levels of plasma steroids with those in urine of lung cancer patients and controls.

5. Proposed starting date: 1st October, 1973.

6. Estimated time to complete: Three Years.

7. Brief description of specific research aims: Previous work by the applicant has shown that lung cancer patients show some abnormalities which are rarely found in normal men in the urinary excretion of some steroids. These abnormalities have been found to be related to the length of survival of both inoperable and surgically treated lung cancer patients. Therefore, it is felt that these results might help to throw some light on the nature of this disease. However, the urinary steroids are the end products of metabolism and excretion of the steroids secreted by the adrenal cortex and the testes. Any interpretation of the urinary findings would be difficult unless the levels of these steroids and their precursors in blood are known. Blood levels of steroids are also essential for tracing the source of the urinary abnormalities.

8. Brief statement of working hypothesis:

The urinary steroid excretion pattern which is abnormal in lung cancer patients reflects abnormalities in plasma steroid concentrations in these patients. The alternative hypothesis which has to be excluded is that the abnormalities in urine are attributable to the abnormalities in the excretion of these steroids by the kidney.

9. Details of experimental design and procedures (append extra pages as necessary)

The main abnormalities in steroid excretion in lung cancer patients are the low androsterone and high 17-hydroxycorticosteroids (17-OHCS), whereas aetiocholanolone is normal (Rao, 1970). The possible significance of these findings in the aetiology or pathogenesis of lung cancer has been discussed (Rao, 1972). The main purpose of the present proposals is to try to trace the source of these abnormalities. Thus, as a first step, it is proposed to measure these steroids or their precursors in blood plasma in a group of lung cancer patients and controls, and compare the steroid pattern in blood with that in urine.

The precursors of the 17-oxosteroids in blood are dehydroepiandrosterone (DHA) and its sulphate from the adrenal cortex, and testosterone from the testes. However, sulphates of DHA and androsterone are the precursors which are found in much larger amounts compared to other precursors of the 17-oxosteroids. The sulphates of DHA and androsterone will be measured by a gas-chromatographic method (De Moor and Heyns, 1966).

It would be very valuable to measure the other precursors of 17-oxosteroids; namely, testosterone and its metabolites in plasma. These steroids include 5α-dihydrotestosterone and androstenedione, but all these three steroids are found in much smaller amounts in blood than the sulphates of androsterone and DHA. Therefore, the former steroids will need more sensitive methods, such as radioimmunoassay. Such assays are in routine use in this laboratory and need chromatographic separation of the individual steroids before quantitation by radioimmunoassay.

The 17-OHCS are derived mainly from cortisol and cortisone secreted by the adrenal cortex, and can be measured as plasma 11-OHCS or 'cortisol' by fluorimetry. A routine method for the measurement of plasma cortisol by competitive protein binding is available in this laboratory, and this method will also be used in some samples as an additional check of the fluorimetric method. The urinary steroids will be measured as was done previously (Rao, 1970).

During the proposed study, it is felt that priority should be given for the determination of the 11-OHCS and the sulphates of androsterone and DHA, because it is known that these steroids are the main precursors of the steroids investigated before in urine. Thus, an early comparison would be possible between plasma and urinary levels. Part of the specimens will be stored at -20°C for the determination of the other steroids by radioimmunoassay as the second part of the study.

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9. Details of experimental design and procedures - CONTINUED:

It is proposed to investigate about 50 lung cancer patients and the same number of chest disease controls and of normal men. Blood and urine specimens would be collected from 100 consecutive patients attending the chest clinic of this Hospital and of other hospitals in this area before a knowledge of diagnosis is established. It is estimated that approximately 50 out of the 100 would have the diagnosis of lung cancer confirmed. Those found not to have lung cancer will be used as chest disease controls for the lung cancer patients. All the laboratory analyses will be carried out 'blind', without a knowledge of diagnosis. General biochemical data, such as liver and kidney function, and also clinical data, will be collected for each patient. It is estimated that the first part of the study would be completed in two years and the second part in one more year.

References:

De Moor and Heyns, W. (1966). In Androgens in Normal and Pathological Conditions. Excerpta Medica Foundation, International Congress Series 101, p.54.

Rao, L.G.S. (1970). Lancet, ii,441.

Rao, L.G.S. (1972). Brit. J. Surg. 59,977.

10. Space and facilities available (when elsewhere than item 2 indicates, state location):

All the equipment required for the proposed study, such as gas-chromatographs, liquid scintillation spectrometers, are already available in this Department.

Bench space is available for one Technician.

An excellent liaison with the chest physiciansand surgeons in this and other hospitals in this area has been established for the past five years, and it is extremely easy to obtain access to patients and controls.

11. Additional facilities required:

None - apart from the staff and other requirements detailed in the budget.

12. Biographical sketches of investigator(s) and other professional personnel (append):

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

14. First year budget:

A. Salaries (give names or state "to be recruited")	% time	Amount (In Pounds Sterling)
Professional (give % time of investigator(s) even if no salary requested)		
Dr. L.G.S. Rao	10%	Nil
Technical		
One Technician	100%	£1,750
Sub-Total for A		£1,750
B. Consumable supplies (by major categories)		
Chemicals, including radioactive isotopes		£250
Glassware and other consumables		£250
Sub-Total for B		£500
C. Other expenses (itemize)		
Secretarial assistance		£500
Travelling expenses to hospitals, other than this Hospital and to attend scientific meetings in Britain		£250
Sub-Total for C		£750
Running Total of A + B + C		£3,000
D. Permanent equipment (itemize)		
1. One ... Single-Pen Recorder, to replace an old recorder used with the gas-chromatograph		£350
2. One ... Deep-Freeze Cabinet		£150
Sub-Total for D		£500
E. Indirect costs (15% of A+B+C)		£450
Total request		£3,950

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	£1,900	£500	£850	-	£500	£3,750
Year 3	£2,000	£500	£950	-	£550	£4,000

16. Other sources of financial support: NONE..... (Currently Active/Pending or Planned).
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name L.G.S. RAO

Signature L.G.S. Rao Date 17th Feb, 1973

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Checks payable to

The Secretary, Board of Management,
Glasgow Royal Infirmary.

Mailing address for checks

Dr. L.G.S. Rao, Department of Steroid
Biochemistry, Royal Infirmary, Glasgow, G4 0SF,
Scotland, U.K.

Responsible officer of institution

Typed Name DR. J.K. GRANT.

Title HEAD OF THE DEPARTMENT OF STEROID BIOCHEMISTRY.

Signature J.K. Grant. Date 23rd Feb, 1973

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CURRICULUM VITAE

Name: L.G.S. Rao.

(Laxmansandra Gundappa Shankara Rao).

Date and Place of Birth: REDACTED REDACTED

Marital Status, etc.: R REDACTED

Qualifications:

1. B.Sc. Hons. (Biochemistry and Botany) - 1949.
   University of Mysore.

2. M.Sc. (Botany) - 1954.
   University of Mysore.

3. M.Sc. (Biochemistry) - 1962.
   University of London.

4. Ph.D. (Biochemistry) - 1966.
   University of Newcastle.

Experience:

1. Lecturer in Biology (1949 - 1953) - University of Travancore.

2. Research Student (September, 1954 - April, 1956) - Department of Biochemistry, Indian Institute of Science, Bangalore.

3. Research Fellow, Indian Council of Medical Research (April, 1956 - September, 1957) - Department of Biochemistry, All-India Institute of Mental Health, Bangalore. The work involved the determination of constituents of body-fluids, including cerebrospinal fluid, paper chromatography of urinary amino acids and their metabolites and agar-gel electrophoresis of serum proteins in chronic schizophrenic patients.

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4. Medical Laboratory Technician (April, 1958 - December, 1959) - Bow and Paddington Group Hospitals, London. Part of this time was spent in participation in research on the effect of androgens on nitrogen and electrolyte balance in patients with disorders of the kidney. I have been recognised as a qualified Medical Laboratory Technician by the Ministry of Health.

5. Hospital Biochemist, Basic Grade (January, 1960 - December, 1962) - Chelsea Hospital for Women, London, S.W.3. Determination of steroid hormones and metabolites in body fluids of patients with endocrine disorders.

6. Junior Research Associate (December, 1962 - December, 1963) - Department of Physiology, The Medical School, University of Newcastle. Research for Ph.D. Degree and teaching of Biochemistry to Science, Dental and Medical Students.

7. Senior Biochemist (April, 1966 - June, 1968) - Psychosomatic Research Unit, Southern General Hospital, Glasgow. Research into Lung Cancer, Heart Disease and Depressive Illness. I was in charge of the biochemistry laboratory and responsible for both the day-to-day running of the laboratory as well as planning the research programme.

8. Lecturer in Biochemistry (July, 1968 - September, 1972) - Department of Psychological Medicine, University of Glasgow, Southern General Hospital, Glasgow, S.W.1. Duties same as in 7.

9. Senior Biochemist (October, 1972 - to date) - Regional Steroid Laboratory, The Royal Infirmary, Glasgow, G4 0SF. Determination of steroid hormones in various disorders in patients of this and other hospitals in this Region.

Publications:

1. Rao, L.G.S. & Taylor, W.
Sex and species differences in conjugate formation during the metabolism of (4-14C) progesterone in vitro. (1963). Biochem. J. 90,30P.

2. Rao, L.G.S. & Taylor, W.
Sex and species differences in conjugate formation during the metabolism of (4-14C) progesterone by liver homogenates. (1965). Biochem. J. 96,172.

3. Rao, L.G.S. & Taylor, W.
Effect of preincubation of homogenate of glucuronide formation during the metabolism of (4-14C) progesterone by male and female rat liver. (1965). Biochem. J. 96,61P.

4. Rao, L.G.S. & Taylor, W.
Glucuronide formation during the metabolism of (4-14C) progesterone by cat-liver homogenate. (1965). Biochem. J. 96,62P.

5. Kissen, D.M. & Rao, L.G.S.
Steroid excretion and personality in lung cancer. (1969). Ann. N.Y. Acad. Sci. 164,476.

6. Rao, L.G.S.
Urinary steroid excretion patterns after acute myocardial infarction. (1970). Lancet, ii,390.

7. Rao, L.G.S.
Discriminant function based on abnormalities in steroid excretion in patients with lung cancer. (1970). Lancet, ii,441.

8. Rao, L.G.S. & Hewit, M.L.
Prognostic significance of a steroid discriminant function in patients with inoperable lung cancer. (1970). Lancet, ii,1063.
See also Editorial on this work on page 1070.

9. Rao, L.G.S.
The concept of lung cancer as an endocrine disease. (1972). Nature, 235,220.

Publications - Continued:

10. Rao, L.G.S.
Effect of resection of lung tumours on the steroid abnormalities in patients with lung cancer. (1971). Brit. Med. J. iv,588.

11. Rao, L.G.S.
Prediction of two-year survival in lung cancer patients by their pre-operative steroid excretion patterns. (1972).
Brit. J. Surgery, 59,977.